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Prophylaxis of thromboembolism during therapy with asparaginase in adults with acute lymphoblastic leukaemia (Protocol)

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[Intervention Protocol]

Prophylaxis of thromboembolism during therapy with asparaginase in adults with acute lymphoblastic leukaemia

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The primary objective is to assess the efficacy and safety of primary thromboprophylaxis for symptomatic VTE in adults with ALL receiving therapy with asparaginase compared with placebo, mechanical thromboprophylaxis, or no thromboprophylaxis. The secondary objective is to compare the efficacy and safety of different groups of primary systemic antithrombotic prophylaxis in adults with ALL receiving therapy with asparaginase by stratifying the main results per type of drug (heparins, vitamin K antagonists, fondaparinux, DOACs, ATIII substitution, cryoprecipitate, FFP).

BACKGROUND

Description of the condition

Acute lymphoblastic leukaemia (ALL) is a serious haematological malignancy with a historically poor survival rate in the adult population (Stock 2013; Toft 2012). However, the event-free survival rates are improving and approaching 75% with the introduction, a decade ago, of paediatric-inspired treatment protocols for younger adults (Toft 2017). Cure rates are challenged by emerging treatment-related toxicities, including thromboembolism (TE), with an incidence that increases with age (Grace 2011; Toft 2016; Truelove 2013). TE has been reported in as many as 41% of adults with ALL during chemotherapy (Grace 2017), compared with 1.4% to 2.2% at the time of ALL diagnosis (De Stefano 2005; Ziegler 2005). Thus, TE rarely occurs at initial presentation of ALL but rather during the initial phases of ALL treatment (Caruso 2007), which most likely indicates a therapeutic relation, including a state of tumour lysis-induced procoagulation.

The backbone of the paediatric-inspired frontline multiagent ALL chemotherapy regimens is based on increased use of non-myelosuppressive agents (glucocorticoids, vincristine, and asparaginase), early and frequent central nervous system prophylaxis, and prolonged maintenance therapy (Boissel 2003; De Bont 2004; Ramanujachar 2007; Stock 2008; Toft 2016). The intensive use of asparaginase, being a key component of the therapy, has been ascribed to the successful outcomes in children with ALL (Raetz 2010). However, as a result of asparagine depletion, its use has been associated with disruption of the balance between haemostatic and fibrinolytic pathways, inducing a procoagulant state. This is mediated by decreased synthesis of the anticoagulant proteins: protein S, protein C, and antithrombin III (ATIII) (Mitchell 1994; Truelove 2013). Additionally, TE has been observed more frequently to coincide with concomitant administration of asparaginase and corticosteroids in children with ALL (Athale 2003; Nowak-Gottl 2001). The impact of these agents, other drugs, and physiologic factors in the pathogenesis of TE remains unknown. Nevertheless, the development of TE during treatment may result in truncation of asparaginase, which has been associated with inferior survival (Silverman 2001).

The majority of TE events are reported to be of venous origin (Athale 2003; Caruso 2007; De Stefano 2005), and apart from age and the treatment regimen other TE risk factors are the malignancy itself, prior TE, infections, immobilisation, central venous catheters, oral contraceptives, inherited thrombophilia traits, smoking, and obesity (Dobromirski 2012; Kahn 2012; Streiff 2011; Truelove 2013). Nevertheless, no recommendations on the use of thromboprophylaxis for adults with ALL exist, as the subgroup at high risk of TE (that could benefit from pre-emptive anticoagulant treatment) has not been clearly defined. In this regard, several different venous thromboembolism (VTE) risk score models have been proposed (Mitchell 2010; Rank 2018; Roininen 2017).

Description of the intervention

This review encompasses the efficacy and safety of primary pre-emptive systemic antithrombotic treatment in adults with ALL during chemotherapy, including asparaginase, compared with placebo, mechanical thromboprophylaxis, or no thromboprophylaxis or comparing different groups of primary systemic antithrombotic prophylaxis.

Currently available drugs for the prevention of VTE include the parenteral anticoagulants unfractionated heparin (UFH) and low molecular weight heparin (LMWH); the oral vitamin K antagonists; the oral synthetic pentasaccharide fondaparinux; the direct oral thrombin inhibitor dabigatran; the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban; and blood-derived products (intravascular ATIII concentrates, cryoprecipitate, or fresh frozen plasma (FFP)). LMWH is usually preferred to vitamin K antagonists in persons receiving concurrent myelosuppressive therapy due to efficacy (Piatek 2012) and as drug interactions, malnutrition, and liver dysfunction lead to fluctuations in the international normalised ratio (INR). UFH is preferable in persons with renal failure or at a high risk of haemorrhage warranting rapid anticoagulation reversal, as the risk of bleeding events increases due to chemotherapy-induced thrombocytopenia. However, heparins introduce the risk of heparin-induced thrombocytopenia and, moreover, rely on ATIII for their mechanism of action, which is usually depleted during asparaginase treatment. In this case, ATIII monitoring and replacement may be necessary to maintain therapeutic anticoagulation. Only limited evidence exists supporting the use of ATIII concentrates in either primary prevention or management following a VTE event (Hunault-Berger 2008). Further, direct oral anticoagulants (DOACs) (dabigatran, rivaroxaban, apixaban, and edoxaban) are potentially a better alternative to LMWH, as they act independently of ATIII and can be administered orally (Sibson 2018), albeit the bleeding risk needs to be balanced against the limited number of approved specific antidotes for DOACs. Consensus suggests that full dose thromboprophylaxis should be administered and is without excessive bleeding risk, when the platelet count is > 50 x 10^9/L (Watson 2015).

Currently available mechanical interventions for the prevention of VTE include intermittent pneumatic compression and graduated elastic stockings.

How the intervention might work

In a meta-analysis, antithrombotic prophylaxis was found to be effective in preventing symptomatic fatal and non-fatal VTE in hospitalised persons at risk of VTE with a non-significant association with major bleeding events (Dentali 2007). Also, a favourable efficacy and safety profile together with a possible survival benefit have been reported regarding use of primary antithrombotic prophylaxis in ambulatory persons with cancer receiving chemotherapy (Maxwell 2012). Moreover, primary antithrombotic prophylaxis with LMWH significantly reduced the incidence of symptomatic VTE in ambulatory persons with cancer treated with chemotherapy in a Cochrane Review (Di Nisio 2014). Additionally, two randomised clinical trials on the use of LMWH prophylaxis in persons with cancer undergoing treatment with chemotherapy found a significant decrease in TE events in the group receiving antithrombotic prophylaxis compared with those receiving placebo or no prophylaxis (Agnelli 2009; Pelzer 2015). Finally, a randomised, placebo-controlled, double-blind clinical trial yielded a significantly lower rate of VTE with apixaban for thromboprophylaxis in ambulatory patients with cancer, who were starting chemotherapy (Carrier 2019).

Current clinical guidelines regarding persons with cancer in general recommend use of primary VTE prophylaxis in individuals undergoing surgery, being hospitalised, and in some ambulatory individuals at high risk for VTE (Kahn 2012; Lyman 2007; Lyman 2013; Lyman 2015; Mandala 2011; Schunemann 2018; Streiff 2011). Herein, the American College of Chest Physicians Evidence-Based Clinical

Practice guidelines recommend prophylaxis with heparins over no prophylaxis in ambulatory persons with solid tumours, additional VTE risk factors (prior VTE, immobilisation, hormonal therapy, and treatment with angiogenesis inhibitors), and at low risk of bleeding (Kahn 2012). Also, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology recommend primary VTE prophylaxis in ambulatory persons with cancer at high risk for VTE (multiple myeloma) (Streiff 2011). Additionally, the American Society of Clinical Oncology guidelines recommend against routine primary VTE prophylaxis in ambulatory persons with cancer receiving chemotherapy with the exception of selected persons at high VTE risk, e.g. individuals with multiple myeloma treated with antiangiogenesis agents combined with chemotherapy and/or dexamethasone; LMWH is the preferred agent of choice (Lyman 2007; Lyman 2013; Lyman 2015). Accordingly, the American Society of Hematology strongly recommend VTE prophylaxis—during hospitalisation only—in acutely or critically ill persons, who have an acceptable bleeding risk. These guidelines recommend against the use of DOACs and recommend use of mechanical prophylaxis in case of unacceptable bleeding risk (Schunemann 2018).

Why it is important to do this review

The improved event-free survival rate in adults with ALL during the last decade may be jeopardised by the incidence of VTE as it is a frequently encountered treatment-related toxicity. VTE introduces a risk of treatment delay, omission, or discontinuation of key antileukaemic agents, e.g. asparaginase, and represents a non-negligible risk of morbidity (Grace 2011) and mortality (Gugliotta 1992; Ku 2009). Evidence-based guidelines for pre-emptive antithrombotic therapy in adults with ALL treated with chemotherapy including asparaginase are lacking, and the efficacy of antithrombotic prophylaxis needs to be balanced against the risks such as (major) bleeding events.

OBJECTIVES

The primary objective is to assess the efficacy and safety of primary thromboprophylaxis for symptomatic VTE in adults with ALL receiving therapy with asparaginase compared with placebo, mechanical thromboprophylaxis, or no thromboprophylaxis. The secondary objective is to compare the efficacy and safety of different groups of primary systemic antithrombotic prophylaxis in adults with ALL receiving therapy with asparaginase by stratifying the main results per type of drug (heparins, vitamin K antagonists, fondaparinux, DOACs, ATIII substitution, cryoprecipitate, FFP).

METHODS

Criteria for considering studies for this review

Types of studies

- Randomised controlled trials (RCTs) including quasi-randomised trials, cross-over trials, and cluster-randomised trials.
- Controlled clinical trials (CCTs).
- Cohort studies and case-control studies; we will include only studies with control groups. Further, we will only include these studies to describe the safety of antithrombotic prophylaxis; we will not include these in the meta-analyses.

Types of participants

Adults with ALL (≥ 18 years of age) treated with chemotherapy including asparaginase.

We will exclude persons < 18 years of age, since another Cochrane Review has already addressed the prevention of VTE in children with cancer and tunnelled central venous catheters (Schoot 2013).

Types of interventions

- Network meta-analysis 1: including trials of all the thromboprophylactic treatments; thus, comparing systemic primary thromboprophylactic treatments (UFH, LMWH, vitamin K antagonists, fondaparinux, dabigatran, rivaroxaban, apixaban, edoxaban, ATIII substitution, cryoprecipitate, FFP), mechanical thromboprophylaxis (intermittent pneumatic compression or graduated elastic stockings), combined thromboprophylaxis, placebo, and no thromboprophylaxis.
- Network meta-analysis 2: including drug trials only; thus, comparing systemic primary prophylactic treatments for the prevention of VTEs (UFH, LMWH, vitamin K antagonists, fondaparinux, dabigatran, rivaroxaban, apixaban, edoxaban, ATIII substitution, cryoprecipitate, FFP) directly (if available) or indirectly by employing placebo-controlled studies as data source.

We will not impose any restrictions on frequency, duration, dosage, intensity, or route of administration.

We will analyse RCTs and non-RCTs separately; only RCTs will be included in the meta-analyses.

Types of outcome measures

Primary outcomes

- All-cause mortality
- Efficacy outcome: symptomatic first-time VTE
  - We will measure efficacy by the reduction of the incidence of symptomatic first-time VTE during ALL treatment with asparaginase until four weeks after the last asparaginase dose (the cutoff time point of measurable pegylated asparaginase activity) (Tram 2017).
- Safety outcome: major bleeding
  - Non-traumatic fatal bleeding and/or symptomatic haemorrhage in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome) and/or bleeding causing a decrease in haemoglobin level of ≥ 20 g/L (1.24 mmol/L) within one day or leading to transfusion of ≥ 2 units of whole blood or red blood cells (Schulman 2005). We will measure safety by the incidence of major bleeding events during treatment with systemic primary prophylactic treatment for the prevention of VTEs.

Secondary outcomes

- The incidence of asymptomatic VTE during ALL treatment with asparaginase until four weeks after the last asparaginase dose.
- Clinically relevant non-major bleeding, defined as any non-traumatic, non-skin bleeding not fulfilling criteria for major bleeding (Schulman 2005), during treatment with systemic primary prophylactic treatment.

- Mortality secondary to a VTE event during ALL treatment with asparaginase until four weeks after the last asparaginase dose.
- Adverse events during treatment with systemic primary prophylactic treatment (e.g. heparin-induced thrombocytopenia for trials using heparins).
- Quality of life assessment during treatment with systemic primary prophylactic treatment using validated tools.

We will group multiple variants of each of the outcome measures into appropriate groups to simplify comparisons, if necessary.

Search methods for identification of studies

Electronic searches

We will search the following electronic databases.

- PubMed/MEDLINE (from 1970 - the time of the introduction of asparaginase in adult ALL treatment - to 2019) (Appendix 1)
- Embase/Ovid (from 1970 to 2019) (Appendix 2)
- Scopus/Elsevier (from 1970 to 2019) (Appendix 3)
- Web of Science Core Collection/Clarivate Analytics (from 1970 to 2019) (Appendix 4)
- The Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, 2019, latest issue) (Appendix 5)

We will not use any filters or restrictions.

The search strategies used for the above mentioned electronic databases will be available in appendices in the review.

- We will use the "Related data—similar articles" option in PubMed/MEDLINE.
- We will use the "Find similar" option of included papers from the search string in Embase/Ovid.
- We will use the "Highly Cited in Field" feature in Web of Science Core Collection.

Searching other resources

Handsearches

Reference lists

- The reference lists of identified studies and related reviews (with awareness of the risk of citation bias)

Trials

- ClinicalTrials.gov registry (www.clinicaltrials.gov)
- The International Standard Randomized Controlled Trial Number (ISRCTN) registry (www.isrctn.com/)
- WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en/)
- Pharmaceutical manufacturers of asparaginase (Shire (pegylated asparaginase), Jazz Pharmaceuticals (Erwinase), Ohara Pharmaceuticals, and Kyowa Pharmaceuticals)

Conference proceedings

- The American Society of Hematology (ASH) (from 1970 to 2019)
- The European Haematology Association (EHA) (from 1994—the year of the first EHA congress—to 2019)
- The American Society of Clinical Oncology (ASCO) (from 1970 to 2019)
- The International Society on Thrombosis and Haemostasis (ISTH) (from 1970 to 2019).

We will include the above mentioned literature from handsearches if we are able to obtain adequate information from either the abstract or personal communication with the authors of the relevant studies. Additionally, we will contact the authors of relevant studies to identify any unpublished material, missing data, or information regarding ongoing studies.

We will not use any filters or restrictions.

Data collection and analysis

We will summarise data in accordance with standard Cochrane methodologies. We will analyse data from different study designs separately (RCTs versus non-RCTs).

Selection of studies

We will upload the results of previously described electronic searches and handsearches to the Covidence systematic review software for screening and study selection (www.covidence.org), and we will remove duplicate records of the same study. Two review authors (C.U.R. and L.S.L.) will independently screen the titles and abstracts of identified articles for eligibility. The two authors will not be blinded to the journal, authors, institution, or results. We will retrieve the full-text of articles judged as potentially eligible by at least one of the review authors. The same two review authors will then independently screen the full-text articles for eligibility using a standardised form with inclusion and exclusion criteria and will resolve potential disagreements by discussion or by consulting a third review author (K.S.). We will not impose any language restrictions. The two review authors will compare reports by author names, location, setting, sample sizes, intervention details, and date in order to detect any duplicate publication. We will contact study authors to resolve any uncertainties. We will make a flow chart of the selection process, create a list of excluded studies (covering all studies that may on the surface appear to meet the eligibility criteria but on further inspection do not), and describe reasons for exclusion of any study considered for this review.

Data extraction and management

Two review authors (C.U.R. and L.S.L.) will independently perform data extraction using a standardised data collection form including the following.

Source

- Study ID (citation ID)
- Report ID
- Review author ID
- Review author ID checking extracted data
- Contact author's details

Study details and methods

- Country
- Number of centres
- Publication type
- Study design
- Total study duration
- Follow-up duration

- Power calculation
- Primary analysis (and definition)
- Stopping rules
- Method of sequence generation (RCTs)
- Allocation concealment (RCTs)
- Blinding of clinicians, participants, and outcome assessors (RCTs)
- Concerns regarding bias
- Confounding factors (baseline confounding factors and co-interventions) (non-RCTs)
- Method of data analysis (methods used to control for confounding and on multiple effect estimates) (non-RCTs)

Participants

- Study inclusion and exclusion criteria
- Total number of participants screened for inclusion
- Method of assigning the intervention (non-RCTs)
- Total number recruited
- Total number excluded
- Total number allocated to each study arm
- Source of study control group and baseline differences between the two groups (non-RCTs)
- Number of allocated participants, who received planned treatment in each treamtment arm
- Number of withdrawals/dropouts in each treatment arm (with reasons)
- Protocol violations
- Missing data
- Demographic and other characteristics (e.g. age, sex, ethnicity, country, comorbidities, TE risk factors)
- Disease and treatment characteristics (e.g. risk group by immunophenotype/cytogenetics/leukaemia burden/central nervous system involvement/treatment response, time from ALL diagnosis, ALL treatment protocol and treatment phase, asparaginase type, route of administration, dosage, frequency and duration (including the time of the last dose), and prior treatment-related toxicities)

Intervention

- Number of study arms
- Antithrombic prophylaxis: type, route of administration, dosage (including cumulative dose), dose reduction (including dose before/after and reason), frequency, truncation (including reason), duration, and timing
- Control group treatment: type, route of administration, dosage (including cumulative dose), dose reduction (including dose before/after and reason), frequency, duration, and timing
- Platelet count and ATIII levels

Outcomes

- Definitions, diagnostic criteria, and diagnostic methods of symptomatic and asymptomatic VTE
- Number of symptomatic VTE events
- Number of asymptomatic VTE events
- Timing of symptomatic VTE events
- Timing of asymptomatic VTE events
- Number of adverse events during antithrombotic prophylaxis treatment (major bleeding events, clinically relevant non-major bleeding, heparin-induced thrombocytopenia)
- Definitions, diagnostic methods, and timing of adverse events
- Number and timing of deaths due to a TE event
- Number and timing of deaths due to bleeding
- Total number of deaths
- Quality of life assessment
- Summary data for each intervention group (e.g. 2×2 table for dichotomous data; means and standard deviations (SDs) for continuous data)

Other

- Key conclusions of the study authors
- Source of funding
- Ethical approvals
- Conflict of interest
- Correspondence required

We will extract all data from studies reported in more than one publication directly into a single data collection form. The two review authors will resolve potential disagreements by discussion or by consulting a third review author. We will contact authors from identified studies for additional information when necessary.

Assessment of risk of bias in included studies

We will assess the risk of bias for RCTs using the Cochrane 'Risk of bias' tool (Higgins 2011a), including the following domains.

- Selection bias (sequence generation and allocation concealment)
- Performance bias (blinding of participants and personnel)
- Detection bias (blinding of outcome assessors)
- Attrition bias (incomplete outcome data)
- Reporting bias (selective outcome reporting)
- Other biases (baseline imbalance, early stopping, bias due to financial interest, academic bias, and bias specifically in relation to cluster-randomised trials and cross-over trials)

We will rate the possible risk of bias in each of the six domains as 'low risk', 'high risk', or 'unclear risk'. We will summarise the risk of bias for each key outcome for each included study. We will judge studies with at least one domain of high risk to be at high risk of bias overall.

Also, we will compare outcomes between trial registrations/protocols and published reports. Where trial registrations/protocols are not available, we will compare outcomes reported in the methods and results sections.

We will evaluate the risk of bias for non-RCTs using the ROBINS-I tool (Sterne 2016) using signalling questions for the following domains.

- Bias due to confounding
- Bias in selection of participants
- Bias in classification of interventions
- Bias due to deviations from intended interventions
- Bias due to missing data

- Bias in measurement of outcomes
- Bias in selection of the reported result

We will use the following response options to the signalling questions: 'yes'; 'probably yes'; 'no'; 'probably no'; and 'no information'. We will rate the possible risk of bias in each of the seven domains as 'low risk', 'moderate risk', 'serious risk', 'critical risk', or 'no information'. We will assess an overall risk of bias for each key outcome for each included study by the following method.

- 'Low risk of bias': the study is judged to be at low risk of bias in all of the tool's seven domains.
- 'Moderate risk of bias': the study is judged to be at low to moderate risk of bias in all of the tool's seven domains.
- 'Serious risk of bias': the study is judged to be at serious risk of bias in at least one of the tool's seven domains.
- 'Critical risk of bias': the study is judged to be at critical risk of bias in at least one of the tool's seven domains.
- 'No information on bias': when information in one or more key domains is lacking.

We have prespecified the following main potential confounding factors.

- Age (variability in the age of persons included; younger adults 18 to 45 years versus older adults > 45 years)
- Adults treated according to paediatric-inspired treatment protocols versus adults treated according to adult treatment protocols
- Sex (male:female ratio)
- VTE risk factors (e.g. prior VTE, infections, immobilisation, central venous catheters, oral contraceptives, pregnancy, inherited thrombophilia traits, smoking, and obesity)
- Comorbidity (e.g. liver disease or renal insufficiency)
- Cumulative dose of asparaginase treatment
- Asparaginase type (*Escherichia coli*-derived versus *Erwinia chrysanthemi*-derived versus pegylated asparaginase)

We will use the GRADE approach to evaluate the quality of evidence (Atkins 2004; Guyatt 2008; Schünemann 2011a), including study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations (e.g. publication bias, plausible confounding, large effect, and dose-response). We will rate the quality of the evidence as 'very low', ;low', 'moderate', or 'high' using the GRADE considerations.

Two review authors (C.U.R. and L.S.L.) will independently assess the methodological quality and quality of the body of evidence of each included study using the above mentioned tools. If a discrepancy between the review authors occurs and no agreement can be reached, a third review author will be involved (K.S.). In the case of insufficient reporting, we will contact study authors for additional information. We will take the evaluated risk of bias in included studies into account when interpreting the results of the review.

The results of the 'Risk of bias' assessments will be available in 'Risk of bias' tables as appendices to the review.

Measures of treatment effect

RCTs

We will use the random-effects model, as we expect that all of the compared interventions do not have the same true effect.

For dichotomous outcomes, we will record the number of events and the total number of participants in both the treatment and control groups. For dichotomous outcomes, we will report the pooled risk ratio (RR) presented with corresponding 95% confidence interval (CI), in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). Where the number of observed events is small (< 5% of sample per group) and where trials have balanced treatment groups, we will report the Peto Odds Ratio (OR) with 95% CI (Deeks 2011).

For continuous outcomes, we will record the mean, SD, and total number of participants in both the treatment and control groups. For continuous outcomes using the same scale, we will perform analyses using the mean difference (MD) with 95% CIs. If continuous outcomes are reported using different scales, we will use standardised mean difference (SMD).
If available, we will extract and report hazard ratios (HRs) for time-to-event-data (VTE, major bleeding due to systemic thromboprophylaxis, mortality secondary to VTE). If HRs are not available, we will estimate the HRs using the Parmar Tierney approach (Parmar 1998; Tierney 2007). If sufficient studies provide HRs, we will use HRs in favour of RRs or MDs in the network meta-analyses; however, we will also perform a separate meta-analysis of data from studies providing only RRs or MDs for the same outcome.

Non-RCTs

For dichotomous outcomes, if available we will extract and report the RR with a 95% CI from statistical analyses adjusting for baseline differences (such as Poisson regressions or logistic regressions) or the ratio of RRs (i.e. the postintervention RR/pre-intervention RR).

For continuous variables, if available we will extract and report the absolute change from a statistical analysis adjusting for baseline differences (such as regression models, mixed models, or hierarchical models), or the relative change adjusted for baseline differences in the outcome measures (i.e. the absolute postintervention difference between the intervention and control groups as well as the absolute pre-intervention difference between the intervention and control groups/the postintervention level in the control group). If data allow, we will undertake quantitative assessments using Review Manager Web (RevMan Web 2019).

All included studies

Where appropriate, we will report the number needed to treat to for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH) with 95% CIs.
If we are not able to report the available data in any of the formats described above, we will perform a narrative report and, if appropriate, we will present the data in tables. We will carry out the statistical analyses using Review Manager Web (RevMan Web 2019), and the statistical computing software R (R 2019).

Unit of analysis issues

We will conduct the analysis at the same level as the allocation for cluster-randomized trials. However, we will seek statistical advise,

if the clusters markedly vary in size potentially leading to unnecessary reduction of the precision of the effect estimate. If available, we will extract a direct estimate of the required effect measure (e.g. an odds ratio with its confidence interval) from an analysis that properly accounts for the cluster design. If the study authors have not conducted such an analysis, we will adjust the results in accordance with the advice given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

We will include and analyse only the first treatment given for cross-over trials, if the wash-out period does not eliminate any carry-over effect of thromboprophylactic drugs regarding elimination half-life, using the standard version of the RoB 2 tool for parallel group randomized trials (Higgins 2019). We will contact the authors of trials reporting only paired analyses (i.e. not reporting data for the first period separately) in order to avoid omission of these and, thus, potential introduction of bias at the meta-analysis level.

If participants are randomised more than once, we will contact the authors of the study to provide us with data associated with the initial randomisation.

For studies with multiple treatment groups, two review authors (C.U.R. and L.S.L.) will exclude subgroups that are considered irrelevant to the analysis. We will tabulate all subgroups in the 'Characteristics of included studies' table. When appropriate, we will combine groups to create a single pairwise comparison. If this is not possible, we will select the most appropriate pair of interventions and exclude the others (Higgins 2011b).

Multiple observations for the same outcome are unlikely to be included in this review.

Dealing with missing data

If data of relevance to the analyses are missing or unclear, we will contact the authors of the concerned study in order to retrieve the missing data. If unsuccessful, our analyses will be based on the number reaching follow-up, and we will perform analyses for worse- and best-case scenarios. We will record the number of persons lost to follow-up for each study.

We will analyse data by intention-to-treat (ITT). If we encounter insufficient data, we will carry out the analyses for each study twice including missing data as success and as failure, respectively. In addition, we will perform an as-treated/per protocol analysis (Higgins 2011b).

Assessment of heterogeneity

We will only consider combining the data and performing network meta-analyses, if the clinical/participant and methodological/study characteristics of individually included studies are sufficiently homogeneous in terms of participants, interventions, and outcomes.

Before conducting the network meta-analyses, we will make sure that all treatments are 'jointly randomisable' for the persons and study settings and carefully evaluate the following.

- Homogeneity within each comparison, e.g. is there a similar participant population or treatment dose?
- Similarity across all comparisons, i.e. are the studies combinable?
- Consistency between the results from direct and indirect comparisons.

Thus, we will assess heterogeneity of the treatment effects between trials within each comparison in the network, evaluating how much variation of treatment effect there is amongst the studies in each comparison by both visual inspection of the forest plots and by using the Chi^2 test with a significance level of $P < 0.1$. We will use the I^2 heterogeneity statistic to help quantify the degree of potential heterogeneity—classifying the results as low (I^2 = 0% to 40%); moderate (I^2 = 30% to 60%); substantial (I^2 = 50% to 90%); and considerable (I^2 = 75% to 100%) heterogeneity across trials (Higgins 2011c). If statistical heterogeneity is considerable, we will not report the overall summary statistic. We will investigate possible reasons for heterogeneity by sensitivity and subgroup analyses (Deeks 2011), if substantial heterogeneity ($I^2 \geq 50\%$) is revealed.

Assessment of reporting biases

We will search multiple electronic databases, conference proceedings, and trial registries for both unpublished and published studies to deal with publication bias, location bias, and time lag bias. We will not impose any limits or language restrictions in the search strategies, thus avoiding language bias. Duplicate reports of the same study will be identified and excluded using the Covidence systematic review software (www.covidence.org) and by comparing authors, location, setting, and sample size in order to avoid duplicate publication bias. We will address selective outcome reporting bias by searching for a trial registration, a protocol, or by scrutinising the methods section for a list of outcomes for comparison with the reported published outcomes regarding each included study.

We will evaluate publication bias and other biases related to small study size by constructing a funnel plot of effect estimates and using a linear regression test for continuous outcomes, if we have a minimum of 10 studies included in the meta-analysis—otherwise the power of the test will be too low to distinguish chance from real asymmetry (Higgins 2011b; Sterne 2011b). We will consider $P < 0.1$ as significant (Sterne 2011a).

Data synthesis

If studies are sufficiently homogenous in their study design, we will conduct two main network meta-analyses according to the recommendations of Cochrane (Cipriani 2013; Deeks 2011; Salanti 2008; Salanti 2011; Salanti 2012), aiming for a ranking of thromboprophylactic treatments using summary outputs from the network meta-analysis.

We aim to conduct two main network meta-analyses as follows.

- Network meta-analysis 1: including trials of all types of approaches to thromboprophylaxis; thus comparing systemic primary thromboprophylactic treatments (UFH, LMWH, vitamin K antagonists, fondaparinux, dabigatran, rivaroxaban, apixaban, edoxaban, antithrombin III (ATIII) substitution), mechanical thromboprophylaxis (intermittent pneumatic compression or graduated elastic stockings), combined thromboprophylaxis, placebo, and no thromboprophylaxis. Of note, we will critically evaluate a potential heterogeneity of the participant populations.
- Network meta-analysis 2: including drug trials only; thus comparing systemic primary prophylactic treatments for the preven-

tion of VTEs (UFH, LMWH, vitamin K antagonists, fondaparinux, dabigatran, rivaroxaban, apixaban, edoxaban, ATIII substitution) directly (if available) or indirectly by employing placebo-controlled studies as data source.

Different thresholds within the comparisons will only be grouped together, if they are considered to be clinically similar. We will analyse the data in RCTs and non-RCTs separately.

RCTs

If a network meta-analysis is feasible, we will pool the data using a random-effects model. For binary outcomes, we will base the estimation of the between-study variance on the Mantel-Haenszel estimator (Deeks 2011). We will use the inverse-variance method for continuous outcomes or outcomes where HRs are available (Deeks 2011); applying the generic inverse-variance facility of Review Manager Web (RevMan Web 2019).

If we find considerable heterogeneity across studies and we identify a cause for the heterogeneity, we will explore this with subgroup analyses. If we cannot find a cause for the heterogeneity, then we will not perform a meta-analysis but comment on the results narratively and present the results from all studies in tables.

Non-RCTs

If a network meta-analysis is feasible for non-RCTs, we will analyse non-RCTs separately. We will only analyse outcomes with adjusted effect estimates, if these are adjusted for the same factors, using the inverse-variance method as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2011).

All included studies

We will use the random-effects model for all analyses, as we anticipate that true effects will be related but will not be the same for included studies. If we cannot perform network meta-analyses, we will comment on the results as a narrative with the results from all studies presented in tables. We will carry out data analyses using Review Manager Web (RevMan Web 2019) and the statistical computing software R (R 2019). We will use R package 'netmeta' for the network meta-analyses.

'Summary of findings' table

We will present a 'Summary of findings' table according to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011a; Schünemann 2011b). We will assess the quality of evidence for each outcome using the GRADE approach (Atkins 2004; Guyatt 2008; Schünemann 2011a) as previously described.

We will include the outcomes listed below in order of most relevant endpoints for participants.

- Efficacy outcome: symptomatic first-time VTE. We will measure efficacy by the reduction in the number of participants with first-time VTE during ALL treatment with asparaginase until four weeks after the last asparaginase dose.
- Safety outcome: major bleeding. We will measure safety by the number of participants with major bleeding during treatment with systemic primary prophylactic treatment.
- Mortality secondary to a VTE event during ALL treatment with asparaginase until four weeks after the last asparaginase dose.
- All-cause mortality.
- Number of participants with clinically relevant non-major bleeding during treatment with systemic primary prophylactic treatment.
- The number of participants with asymptomatic VTE during ALL treatment with asparaginase until four weeks after the last asparaginase dose.
- Adverse events during treatment with systemic primary prophylactic treatment (e.g. heparin-induced thrombocytopenia for trials using heparins).
- Quality of life during treatment with systemic primary prophylactic treatment.

Subgroup analysis and investigation of heterogeneity

If adequate data are available, we will perform subgroup analyses for each of the following outcomes in order to assess the effect on heterogeneity.

- RCTs/quasi-randomised trials versus cross-over trials/cluster-randomised trials
- Type of antithrombotic prophylaxis (heparins versus all other types)
- Adults treated according to paediatric-inspired treatment protocols versus adults treated according to adult treatment protocols
- Participants with versus without inherited thrombophilia traits
- Participants with versus without central venous catheters
- Cumulative dose of asparaginase treatment
- Asparaginase type (*Escherichia coli*-derived versus *Erwinia chrysanthemi*-derived versus pegylated asparaginase)

Sensitivity analysis

We will assess the robustness of the results by performing the following sensitivity analyses, when possible.

- Fixed-effect meta-analysis—as large differences in estimated effects indicate small study effects.
- Including studies with a 'low risk of bias' (e.g. RCTs with methods assessed as low risk for random sequence generation and concealment of treatment allocation) in a new sensitivity meta-analysis.
- Including studies with less than a 20% dropout in a new sensitivity meta-analysis.

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APPENDICES

Appendix 1. PubMed/MEDLINE search strategy

1. For **ALL patients**, the following MeSH headings and text words were used:

"precursor cell lymphoblastic leukemia-lymphoma"[MeSH] OR "acute lymphoblastic leukemia"[Text Word] OR "acute lymphoblastic leukaemia"[Text Word] OR "acute lymphatic leukemia"[Text Word] OR "acute lymphatic leukaemia"[Text Word] OR "acute lymphocytic leukemia"[Text Word] OR "acute lymphocytic leukaemia"[Text Word] OR "acute lymphoid leukemia"[Text Word] OR "acute lymphoid leukaemia"[Text Word] OR "acute lymphocyte leukemia"[Text Word] OR "precursor cell lymphoblastic leukemia"[Text Word] OR "precursor cell lymphoblastic leukaemia"[Text Word] OR "B-cell lymphoblastic leukemia"[Text Word] OR "B-cell lymphoblastic leukaemia"[Text Word] OR "T-cell lymphoblastic leukemia"[Text Word] OR "T-cell lymphoblastic leukaemia"[Text Word] OR "pre-B cell leukemia"[Text Word] OR "pre-B cell leukaemia"[Text Word] OR "acute B-cell leukemia"[Text Word] OR "acute B-cell leukaemia"[Text Word] OR "acute T-cell leukemia"[Text Word] OR "acute T-cell leukaemia"[Text Word] OR "pre-B cell ALL"[Text Word] OR "pre-B ALL"[Text Word] OR "BCP-ALL"[Text Word] OR "B-cell ALL"[Text Word] OR "B-ALL"[Text Word] OR "T-cell ALL"[Text Word] OR "T-ALL"[Text Word]

2. For **intervention**, the following MeSH headings and text words were used:

anticoagulants[MeSH] OR coumarins[MeSH] OR phenindione[MeSH] OR heparin[MeSH] OR dabigatran[MeSH] OR "hirudin therapy"[MeSH] OR rivaroxaban[MeSH] OR "antithrombin III"[MeSH] OR antithrombins[MeSH] OR "platelet aggregation inhibitors"[MeSH] OR "phosphodiesterase inhibitors"[MeSH] OR tetrazoles[MeSH] OR thienopyridines[MeSH] OR "prasugrel hydrochloride"[MeSH] OR aspirin[MeSH] OR dipyridamole[MeSH] OR warnerin[Supplementary Concept] OR certoparin[Supplementary Concept] OR fondaparinux[Supplementary Concept] OR ximelagatran[Supplementary Concept] OR idraparinux[Supplementary Concept] OR lepirudin[Supplementary Concept] OR argatroban[Supplementary Concept] OR bivalirudin[Supplementary Concept] OR apixaban[Supplementary Concept] OR edoxaban[Supplementary Concept] OR betrixaban[Supplementary Concept] OR otamixaban[Supplementary Concept] OR darexaban[Supplementary Concept] OR eisenstasin[Supplementary Concept] OR inogatran[Supplementary Concept] OR clopidogrel[Supplementary Concept] OR ticagrelor[Supplementary Concept] OR elinogrel[Supplementary Concept] OR cangrelor[Supplementary Concept] OR terutroban[Supplementary Concept] OR triflusal[Supplementary Concept] OR cilostazol[Supplementary Concept] OR satigrel[Supplementary Concept] OR vorapaxar[Supplementary Concept] OR indobufen[Supplementary Concept] OR "CY 222"[Supplementary Concept] OR "Ave 5026"[Supplementary Concept] OR BIBR-953[Supplementary Concept] OR AZD-0837[Supplementary Concept] OR LY517717[Supplementary Concept] OR GW813893[Supplementary Concept] OR TAK442[Supplementary Concept] OR PD0348292[Supplementary Concept] OR prevention[Text Word] OR preventive*[Text Word] OR prophylaxis[Text Word] OR prophylactic*[Text Word] OR thromboprophylaxis[Text Word] OR antithrombotic*[Text Word] OR anticoagulant*[Text Word] OR vitamin K antagonist*[Text Word] OR warfarin[Text Word] OR waran[Text Word] OR marevan[Text Word] OR marcoumar[Text Word] OR marcumar[Text Word] OR phenprocoumon[Text Word] OR acenocoumarol[Text Word] OR nicoumalone[Text Word] OR aldocumar[Text Word] OR sintrom[Text Word] OR sinthrome[Text Word] OR fenprocoumon[Text Word] OR falithrom[Text Word] OR jantoven[Text Word] OR 4-hydroxycoumarin*[Text Word] OR coumadin[Text Word] OR coumarin*[Text Word] OR phenindione[Text Word] OR warnerin[Text Word] OR heparin*[Text Word] OR dalteparin[Text Word] OR enoxaparin*[Text Word] OR nadroparin*[Text Word] OR tinzaparin[Text Word] OR fraxiparin*[Text Word] OR clexane[Text Word] OR klexane[Text Word] OR lovenox[Text Word] OR fragmin[Text Word] OR ardeparin[Text Word] OR normiflo[Text Word] OR logiparin[Text Word] OR innohep[Text Word] OR certoparin[Text Word] OR sandoparin[Text Word] OR reviparin[Text Word] OR clivarin[Text Word] OR danaproid[Text Word] OR danaparoid[Text Word] OR orgaran[Text Word] OR bemiparin[Text Word] OR hibor[Text Word] OR zibor[Text Word] OR badyket[Text Word] OR semuloparin[Text Word] OR parnaparin[Text Word] OR fluxum[Text Word] OR liquaemin[Text Word] OR liquemin[Text Word] OR tedelparin[Text Word] OR lomoparan[Text Word] OR factor Xa inhibitor*[Text Word] OR fondaparinux[Text Word] OR arixtra[Text Word] OR ximelagatran[Text Word] OR exanta[Text Word] OR melagatran[Text Word] OR idraparinux[Text Word] OR oral direct inhibitor*[Text Word] OR pradaxa[Text Word] OR dabigatran[Text Word] OR rendix[Text Word] OR lepirudin[Text Word] OR hirudin*[Text Word] OR argatroban[Text Word] OR bivalirudin[Text Word] OR rivaroxaban[Text Word] OR xarelto[Text Word] OR apixaban[Text Word] OR eliquis[Text Word] OR edoxaban[Text Word] OR lixiana[Text Word] OR betrixaban[Text Word] OR otamixaban[Text Word] OR darexaban[Text Word] OR eisenstasin[Text Word] OR inogatran[Text Word] OR antithrombin*[Text Word] OR atenativ[Text Word] OR thrombin inhibitor*[Text Word] OR ariven[Text Word] OR hepalean[Text Word] OR lipo-hepin[Text Word] OR antixarin[Text Word] OR embolex[Text Word] OR sofarin[Text Word] OR antiplatelet*[Text Word] OR platelet inhibitor*[Text Word] OR platelet antagonist*[Text Word] OR thrombocyte inhibitor*[Text Word] OR thienopyridine[Text Word] OR ticlopidine[Text Word] OR ticlid[Text Word] OR clopidogrel[Text Word] OR plavix[Text Word] OR prasugrel[Text Word] OR efient[Text Word] OR effient[Text Word] OR ticagrelor[Text Word] OR brilinta[Text Word] OR elinogrel[Text Word] OR cangrelor[Text Word] OR terutroban[Text Word] OR triplion[Text Word] OR aspirin*[Text Word] OR "acetylsalicylic acid"[Text Word] OR triflusal[Text Word] OR disgren[Text Word] OR cilostazol[Text Word] OR pletal[Text Word] OR pletaal[Text Word] OR dipyridamol*[Text Word] OR persantine[Text Word] OR picotamide[Text Word] OR satigrel[Text Word] OR vorapaxar[Text Word] OR indobufen[Text Word] OR"CY 222"[Text Word] OR KABI-2165[Text Word] OR "KABI 2165"[Text Word] OR Emt-966[Text Word] OR Emt-967[Text Word] OR PK-10169[Text Word] OR PK10169[Text Word] OR FR-860[Text Word] OR CY-216[Text Word] OR CY216[Text Word] OR "Ave 5026"[Text Word] OR Ave5026[Text Word] OR M118[Text Word] OR BIBR-953[Text Word] OR BIBR-1048[Text Word] OR AZD-0837[Text Word] OR AZD0837[Text Word] OR S35972[Text Word] OR Bay-597939[Text Word] OR PRT-054021[Text Word] OR PRT054021[Text Word] OR BMS-562247[Text Word] OR DU-176b[Text Word] OR DU176b[Text Word] OR YM-150[Text Word] OR YM150[Text Word] OR LY-517717[Text Word] OR LY517717[Text Word] OR GW813893[Text Word] OR TAK-442[Text Word] OR PD0348292[Text Word] OR AZD6140[Text Word] OR PRT-060128[Text Word] OR PRT060128[Text Word] OR SCH-530348[Text Word] OR SCH530348[Text Word] OR E5555[Text Word] OR OPC-13013[Text Word]

3. For **VTE**, the following MeSH headings and text words were used:

"embolism and thrombosis"[MeSH] OR thrombotic*[Text Word] OR thromboemboli*[Text Word] OR thrombosis[Text Word] OR embolism[Text Word] OR "blood clot"[Text Word]

Final search: 1 AND 2 AND 3

[MeSH = MeSH term; * = zero or more characters]

Appendix 2. Embase/Ovid search strategy

1. For **ALL patients**, the following Emtree terms and text words were used:

exp acute lymphoblastic leukemia/ OR pre-B-cell leukemia/ OR pre-B-cell leukaemia/ OR acute B-cell leukemia/ OR acute B-cell leukaemia/ OR acute T-cell leukemia/ OR acute T-cell leukaemia/ OR pre-B-cell ALL.mp. OR pre-B-ALL.mp. OR BCP-ALL.mp. OR B-cell ALL.mp. OR B-ALL.mp. OR T-cell ALL.mp. OR T-ALL.mp. OR B-cell lymphoblastic leukemia.mp. OR B-cell lymphoblastic leukaemia.mp. OR T-cell lymphoblastic leukemia.mp. OR T-cell lymphoblastic leukaemia.mp. OR pre-B cell leukemia.mp. OR pre-B cell leukaemia.mp. OR ((acute OR precur-

sor) adj3 (lymphocyte OR lymphocytic OR lymphatic OR lymphoblastic OR lymphoid OR lymphocyte OR T-cell OR B-cell) adj (leukemia OR leukaemia)).mp.

2. For **intervention**, the following Emtree terms and text words were used:

exp prophylaxis/ OR exp anticoagulant agent/ OR exp anticoagulant therapy/ OR exp coumarin derivative/ OR exp ardeparin/ OR exp thienopyridine derivative/ OR exp triflusal/ OR prevention.mp. OR preventive$.mp. OR prophylaxis.mp. OR prophylactic$ OR thromboprophylaxis.mp. OR antithrombotic$.mp. OR anticoagulant$.mp. OR vitamin K antagonist$.mp. OR warfarin.mp. OR lawarin.mp. OR waran.mp. OR marevan.mp. OR jantoven.mp. OR coumadin.mp. OR coumarin$.mp. OR phenindione.mp. OR carfin.mp. OR kumatox.mp. OR prothromadin.mp. OR tedicumar.mp. OR tintorane.mp. OR warfant.mp. OR warfilone.mp. OR warnerin.mp. OR phenprocoumon.mp. OR fenprocoumon.mp. OR marcoumar.mp. OR marcumar.mp. OR 4-hydroxycoumarins.mp. OR phenprocouman.mp. OR falithrom.mp. OR liquaemin.mp. OR liquemin.mp. OR acenocoumarol.mp. OR nicoumalone.mp. OR aldocumar.mp. OR sintrom.mp. OR sinthrome.mp. OR heparin$.mp. OR dalteparin.mp. OR fragmin$.mp. OR enoxaparin$.mp. OR clexane.mp. OR klexane.mp. OR lovenox.mp. OR nadroparin $.mp. OR fraxiparin$.mp. OR tinzaparin.mp. OR innohep.mp. OR logiparin.mp. OR ardeparin.mp. OR normiflo.mp. OR certoparin.mp. OR badyket.mp. OR sandoparin.mp. OR reviparin.mp. OR clivarin.mp. OR danaproid.mp. OR danaparoid.mp. OR orgaran.mp. OR bemiparin.mp. OR hibor.mp. OR zibor.mp. OR semuloparin.mp. OR parnaparin.mp. OR fluxum.mp. OR lohepa.mp. OR lowhepa.mp. OR tedelparin.mp. OR thromboliquine.mp. OR lomoparan.mp. OR factor Xa inhibitor$.mp. OR fondaparinux.mp. OR arixtra.mp. OR quixidar.mp. OR ximelagatran.mp. OR exanta.mp. OR exarta.mp. OR melagatran.mp. OR idraparinux.mp. OR dabigatran.mp. OR rendix.mp. OR oral direct inhibitor$.mp. OR pradaxa.mp. OR lepirudin.mp. OR hirudin$.mp. OR argatroban.mp. OR bivalirudin.mp. OR rivaroxaban.mp. OR xarelto.mp. OR apixaban.mp. OR eliquis.mp. OR edoxaban.mp. OR lixiana.mp. OR betrixaban.mp. OR otamixaban.mp. OR darexaban.mp. OR eisenstasin.mp. OR inogatran.mp. OR atenativ.mp. OR antithrombin$.mp. OR thrombin inhibitor$.mp. OR ariven.mp. OR arteven.mp. OR calcilean.mp. OR hepalean.mp. OR hepathrom.mp. OR leparan.mp. OR lipo-hepin.mp. OR pabyrin.mp. OR pularin.mp. OR antixarin.mp. OR embolex.mp. OR mono-embolex.mp. OR sofarin.mp. OR antiplatelet$.mp. OR platelet inhibitor$.mp. OR platelet antagonist$.mp. OR thrombocyte inhibitor$.mp. OR thrombocyte antagonist$.mp. OR thienopyridine.mp. OR ticlopidine.mp. OR ticlid.mp. OR clopidogrel.mp. OR plavix.mp. OR prasugrel.mp. OR efient.mp. OR effient.mp. OR prasita.mp. OR ticagrelor.mp. OR brilinta.mp. OR elinogrel.mp. OR cangrelor.mp. OR terutroban.mp. OR triplion.mp. OR aspirin$.mp. OR acetylsalicylic acid.mp. OR triflusal.mp. OR disgren.mp. OR cilostazol.mp. OR pletal.mp. OR pletaal.mp. OR dipyridamole$.mp. OR persantine.mp. OR picotamide.mp. OR picotinamide.mp. OR satigrel.mp. OR vorapaxar.mp. OR indobufen.mp. OR CY222.mp. OR RD11885.mp. OR KABI2165.mp. OR Emt966.mp. OR Emt967.mp. OR Emt977.mp. OR PK10169.mp. OR FR860.mp. OR CY216.mp. OR KB101.mp. OR OP2123.mp. OR OP2133.mp. OR Ave5026.mp. OR M118.mp. OR BIBR953.mp. OR BIBR1048.mp. OR AZD0837.mp. OR S35972.mp. OR Bay597939.mp. OR PRT054021.mp. OR BMS562247.mp. OR DU176b.mp. OR YM150.mp. OR LY517717.mp. OR GW813893.mp. OR TAK442.mp. OR PD0348292.mp. OR GSK813893.mp. OR AZD6140.mp. OR PRT060128.mp. OR ARC6993.mp. OR SCH530348.mp. OR E5555.mp. OR OPC13013.mp.

3. For **VTE**, the following Emtree terms and text words were used:

exp thromboembolism/ OR thrombotic$.mp. OR thromboemboli$.mp. OR thrombosis.mp. OR embolism.mp. OR blood clot$.mp.

Final search: 1 AND 2 AND 3

[exp = explode; mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, and candidate term word; $ = zero or more characters; / = Emtree term including all subject headings]

Appendix 3. Scopus/Elsevier search strategy

1. For **ALL patients**, the following text words were used:

TITLE-ABS-KEY(pre-B-cell ALL OR pre-B ALL OR BCP-ALL OR B-cell ALL OR B-ALL OR T-cell ALL OR T-ALL OR “B-cell lymphoblastic leukemia” OR “B-cell lymphoblastic leukaemia” OR “T-cell lymphoblastic leukemia” OR “T-cell lymphoblastic leukaemia” OR “pre-B cell leukemia” OR “pre-B cell leukaemia”) OR TITLE-ABS-KEY((acute OR precursor) W/3 (lymphocyte OR lymphocytic OR lymphatic OR lymphoblastic OR lymphoid OR lymphocyte OR T-cell OR B-cell) W/ (leukemia OR leukaemia))

2. For **intervention**, the following text words were used:

TITLE-ABS-KEY(prevention OR *preventive OR *prophylactic OR prophylaxis OR thromboprophylaxis OR *antithrombotic OR *anticoagulant OR “vitamin K antagonist” OR warfarin OR lawarin OR waran OR marevan OR marcoumar OR marcumar OR phenprocoumon OR acenocoumarol OR nicoumalone OR aldocumar OR sintrom OR sinthrome OR fenprocoumon OR falithrom OR jantoven OR 4-hydroxycoumarins OR coumadin OR *coumarin OR phenindione OR carfin OR kumatox OR prothromadin OR tedicumar OR tintorane OR warfant OR warfilone OR warnerin OR *heparin OR dalteparin OR *enoxaparin OR *nadroparin OR tinzaparin OR fraxiparin OR fraxiparine OR clexane OR klexane OR lovenox OR fragmin OR ardeparin OR normiflo OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR danaparoid OR orgaran OR bemiparin OR hibor OR zibor OR badyket OR semuloparin OR parnaparin OR fluxum OR lohepa OR lowhepa OR liquaemin OR liquemin OR tedelparin OR thromboliquine OR lomoparan OR “factor Xa inhibitor” OR fondaparinux OR arixtra OR quixidar OR ximelagatran OR exanta OR exarta OR melagatran OR idraparinux OR “oral direct inhibitor” OR pradaxa OR dabigatran OR rendix OR lepirudin OR *hirudin OR argatroban OR bivalirudin OR rivaroxaban OR xarelto OR apixaban OR eliquis OR

edoxaban OR lixiana OR betrixaban OR otamixaban OR darexaban OR eisenstasin OR inogatran OR *antithrombin OR atenativ OR "thrombin inhibitor" OR ariven OR arteven OR calcilean OR hepalean OR hepathrom OR leparan OR lipo-hepin OR pabyrin OR pularin OR antixarin OR embolex OR mono-embolex OR sofarin OR *antiplatelet OR "platelet inhibitor" OR "platelet antagonist" OR "thrombocyte inhibitor" OR "thrombocyte antagonist" OR thienopyridine OR ticlopidine OR ticlid OR clopidogrel OR plavix OR prasugrel OR efient OR effient OR prasita OR ticagrelor OR brilinta OR elinogrel OR cangrelor OR terutroban OR triplion OR *aspirin OR "acetylsalicylic acid" OR triflusal OR disgren OR cilostazol OR pletal OR pletaal OR *dipyridamole OR persantine OR picotamide OR picotinamide OR satigrel OR vorapaxar OR indobufen OR "CY 222" OR "RD 11885" OR RD11885 OR KABI-2165 OR "KABI 2165" OR Emt-966 OR Emt966 OR Emt-967 OR Emt977 OR PK-10169 OR PK10169 OR FR-860 OR FR860 OR CY-216 OR CY216 OR KB101 OR "OP 2123" OR OP2133 OR "Ave 5026" OR Ave5026 OR M118 OR BIBR-953 OR BIBR953 OR BIBR-1048 OR BIBR1048 OR AZD-0837 OR AZD0837 OR S-35972 OR S35972 OR Bay-597939 OR Bay597939 OR PRT-054021 OR PRT054021 OR BMS-562247 OR DU-176b OR DU176b OR YM-150 OR YM150 OR LY-517717 OR LY517717 OR GW813893 OR TAK-442 OR TAK442 OR PD0348292 OR GSK-813893 OR GSK813893 OR AZD6140 OR PRT-060128 OR PRT060128 OR AR-C6993 OR ARC6993 OR SCH-530348 OR SCH530348 OR E5555 OR OPC-13013 OR OPC13013)

3. For **VTE**, the following text words were used:

TITLE-ABS-KEY(*thrombotic OR *thromboemboli OR thrombosis OR embolism OR "blood clot")

Final search: 1 AND 2 AND 3

[TITLE-ABS-KEY = title, abstract, and keywords]

Appendix 4. Web of Science Core Collection/Clarivate Analytics search strategy

1. For **ALL patients**, the following text words were used:

TS=(pre-B-cell ALL OR pre-B ALL OR BCP-ALL OR B-cell ALL OR B-ALL OR T-cell ALL OR T-ALL OR "B-cell lymphoblastic leukemia" OR "B-cell lymphoblastic leukaemia" OR "T-cell lymphoblastic leukemia" OR "T-cell lymphoblastic leukaemia" OR "pre-B cell leukemia" OR "pre-B cell leukaemia") OR TS=((acute OR precursor) NEAR/3 (lymphocyte OR lymphocytic OR lymphatic OR lymphoblastic OR lymphoid OR lymphocyte OR T-cell OR B-cell) NEAR/1 (leukemia OR leukaemia))

2. For **intervention**, the following text words were used:

TS=(prevention OR preventive* OR prophylactic* OR prophylaxis OR thromboprophylaxis OR antithrombotic* OR anticoagulant* OR vitamin K antagonist* OR warfarin OR lawarin OR waran OR marevan OR marcoumar OR marcumar OR phenprocoumon OR acenocoumarol OR nicoumalone OR aldocumar OR sintrom OR sinthrome OR fenprocoumon OR falithrom OR jantoven OR 4-hydroxycoumarins OR coumadin OR coumarin* OR phenindione OR carfin OR kumatox OR prothromadin OR tedicumar OR tintorane OR warfant OR warfilone OR warnerin OR heparin* OR dalteparin OR enoxaparin* OR nadroparin* OR tinzaparin OR fraxiparin OR fraxiparine OR clexane OR klexane OR lovenox OR fragmin OR ardeparin OR normiflo OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR danaparoid OR orgaran OR bemiparin OR hibor OR zibor OR badyket OR semuloparin OR parnaparin OR fluxum OR lohepa OR lowhepa OR liquaemin OR liquemin OR tedelparin OR thromboliquine OR lomoparan OR factor Xa inhibitor* OR fondaparinux OR arixtra OR quixidar OR ximelagatran OR exanta OR exarta OR melagatran OR idraparinux OR oral direct inhibitor* OR pradaxa OR dabigatran OR rendix OR lepirudin OR hirudin* OR argatroban OR bivalirudin OR rivaroxaban OR xarelto OR apixaban OR eliquis OR edoxaban OR lixiana OR betrixaban OR otamixaban OR darexaban OR eisenstasin OR inogatran OR antithrombin* OR atenativ OR thrombin inhibitor* OR ariven OR arteven OR calcilean OR hepalean OR hepathrom OR leparan OR lipo-hepin OR pabyrin OR pularin OR antixarin OR embolex OR mono-embolex OR sofarin OR antiplatelet* OR platelet inhibitor* OR platelet antagonist* OR thrombocyte inhibitor* OR thrombocyte antagonist* OR thienopyridine OR ticlopidine OR ticlid OR clopidogrel OR plavix OR prasugrel OR efient OR effient OR prasita OR ticagrelor OR brilinta OR elinogrel OR cangrelor OR terutroban OR triplion OR aspirin* OR "acetylsalicylic acid" OR triflusal OR disgren OR cilostazol OR pletal OR pletaal OR dipyridamole* OR persantine OR picotamide OR picotinamide OR satigrel OR vorapaxar OR indobufen OR "CY 222" OR "RD 11885" OR RD11885 OR KABI-2165 OR "KABI 2165" OR Emt-966 OR Emt966 OR Emt-967 OR Emt977 OR PK-10169 OR "PK10169" OR FR-860 OR FR860 OR CY-216 OR CY216 OR KB101 OR "OP 2123" OR OP2133 OR "Ave 5026" OR Ave5026 OR M118 OR BIBR-953 OR BIBR953 OR BIBR-1048 OR "BIBR1048" OR AZD-0837 OR AZD0837 OR S-35972 OR S35972 OR Bay-597939 OR Bay597939 OR PRT-054021 OR PRT054021 OR BMS-562247 OR DU-176b OR DU176b OR YM-150 OR YM150 OR LY-517717 OR LY517717 OR GW813893 OR TAK-442 OR TAK442 OR PD0348292 ORGSK-813893 OR GSK813893 OR AZD6140 OR PRT-060128 OR PRT060128 OR AR-C6993 OR ARC6993 OR SCH-530348 OR SCH530348 OR E5555 OR OPC-13013 OR OPC13013)

3. For **VTE**, the following text words were used:

TS=(thrombotic* OR thromboemboli* OR embolism OR thrombosis OR "blood clot")

Final search: 1 AND 2 AND 3

[TS = topic field including title, abstract, and keywords]

Appendix 5. The Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

1. For **ALL patients**, the following text words were used:

#a: MeSH descriptor: [Precursor Cell Lymphoblastic Leukemia-Lymphoma] explode all trees

#b: ("acute lymphoblastic leukemia" OR "acute lymphatic leukemia" OR "acute lymphocytic leukemia" OR "acute lymphoid leukemia" OR "acute lymphocyte leukemia" OR "precursor cell lymphoblastic leukemia" OR "B-cell lymphoblastic leukemia" OR "T-cell lymphoblastic leukemia" OR "pre-B cell leukemia" OR "acute B-cell leukemia" OR "acute T-cell leukemia" OR "pre-B cell ALL" OR "pre-B ALL" OR "BCP-ALL" OR "B-cell ALL" OR "B-ALL" OR "T-cell ALL" OR T-ALL);ti,ab,kw

#1: a OR b

2. For **intervention**, the following text words were used:

#a: MeSH descriptor: [Anticoagulants] explode all trees

#b: MeSH descriptor: [Coumarins] explode all trees

#c: MeSH descriptor: [Phenindione] explode all trees

#d: MeSH descriptor: [Heparin] explode all trees

#e: MeSH descriptor: [Dabigatran] explode all trees

#f: MeSH descriptor: ["Hirudin therapy"] explode all trees

#g: MeSH descriptor: [Rivaroxaban] explode all trees

#h: MeSH descriptor: [Antithrombin III] explode all trees

#i: MeSH descriptor: [Antithrombins] explode all trees

#j: MeSH descriptor: [Platelet aggregation inhibitors] explode all trees

#k: MeSH descriptor: [Phosphodiesterase inhibitors] explode all trees

#l: MeSH descriptor: [Tetrazoles] explode all trees

#m: MeSH descriptor: [Thienopyridines] explode all trees

#n: MeSH descriptor: [Prasugrel hydrochloride] explode all trees

#o: MeSH descriptor: [Aspirin] explode all trees

#p: MeSH descriptor: [Dipyridamole] explode all trees

#q: (prevention OR preventive* OR prophylaxis OR prophylactic* OR thromboprophylaxis OR antithrombotic* OR anticoagulant* OR "vitamin K antagonist" OR warfarin OR lawarin OR waran OR marevan OR marcoumar OR marcumar OR phenprocoumon OR acenocoumarol OR nicoumalone OR aldocumar OR sintrom OR sinthrome OR fenprocoumon OR falithrom OR jantoven OR coumadin OR coumarin* OR phenindione OR carfin OR kumatox OR prothromadin OR tedicumar OR tintorane OR warfant OR warfilone OR warnerin OR heparin* OR dalteparin OR enoxaparin* OR nadroparin* OR tinzaparin OR fraxiparin OR fraxiparine OR clexane OR klexane OR lovenox OR fragmin OR ardeparin OR normiflo OR logiparin OR innohep OR certoparin OR sandoparin OR reviparin OR clivarin OR danaproid OR danaparoid OR orgaran OR bemiparin OR hibor OR zibor OR badyket OR semuloparin OR parnaparin OR fluxum OR lohepa OR lowhepa OR liquaemin OR liquemin OR tedelparin OR thromboliquine OR lomoparan OR "factor Xa inhibitor" OR fondaparinux OR arixtra OR quixidar OR ximelagatran OR exanta OR exarta OR melagatran OR idraparinux OR "oral direct inhibitor" OR pradaxa OR dabigatran OR rendix OR lepirudin OR hirudin* OR argatroban OR bivalirudin OR rivaroxaban OR xarelto OR apixaban OR eliquis OR edoxaban OR lixiana OR betrixaban OR otamixaban OR darexaban OR eisenstasin OR inogatran OR antithrombin* OR atenativ OR "thrombin inhibitor" OR ariven OR arteven OR calcilean OR hepalean OR hepathrom OR leparan OR lipo-hepin OR pabyrin OR pularin OR antixarin OR embolex OR mono-embolex OR sofarin OR antiplatelet* OR "platelet inhibitor" OR "platelet antagonist" OR "thrombocyte inhibitor" OR "thrombocyte antagonist" OR thienopyridine OR ticlopidine OR ticlid OR clopidogrel OR plavix OR prasugrel OR efient OR effient OR prasita OR ticagrelor OR brilinta OR elinogrel OR cangrelor OR terutroban OR triplion OR aspirin* OR "acetylsalicylic acid" OR triflusal OR disgren OR cilostazol OR pletal OR pletaal OR dipyridamol* OR persantine OR picotamide OR picotinamide OR satigrel OR vorapaxar OR indobufen OR "CY 222" OR "RD 11885" OR RD11885 OR KABI-2165 OR "KABI 2165" OR Emt-966 OR Emt966 OR Emt-967 OR Emt977 OR PK-10169 OR "PK10169" OR FR-860 OR FR860 OR CY-216 OR CY216 OR KB101 OR "OP 2123" OR OP2133 OR "Ave 5026" OR Ave5026 OR M118 OR BIBR-953 OR BIBR953 OR BIBR-1048 OR "BIBR1048" OR AZD-0837 OR AZD0837 OR S-35972 OR S35972 OR Bay-597939 OR Bay597939 OR PRT-054021 OR PRT054021 OR BMS-562247 OR DU-176b OR DU176b OR YM-150 OR YM150 OR LY-517717 OR LY517717 OR GW813893 OR TAK-442 OR TAK442

OR PD0348292 OR GSK-813893 OR GSK813893 OR AZD6140 OR PRT-060128 OR PRT060128 OR AR-C6993 OR ARC6993 OR SCH-530348 OR SCH530348 OR E5555 OR OPC-13013 OR OPC13013);ti,ab,kw

#2: a OR b OR c OR d OR e OR f OR g OR h OR i OR j OR k OR l OR m OR n OR o OR p OR q

3. For **VTE**, the following text words were used:

#a: MeSH descriptor: [Embolism and Thrombosis] explode all trees

#b: (thrombotic* OR thromboemboli* OR thrombosis OR embolism OR "blood clot");ti,ab,kw

#3: a OR b

Final search: 1 AND 2 AND 3

[ti = title; ab = abstract; kw = keyword; * = zero or more characters]

WHAT'S NEW

Date	Event	Description
16 October 2019	Amended	The amendments are listed in the following: 1. Methods section–Types of studies: We will include cross-over RCTs and cluster-randomised trials. Appropriate precautions will be made: First, if the wash-out period does not eliminate any carry-over effect of thromboprophylactic drugs regarding elimination half-life, we will include and analyse only the first treatment given for cross-over trials. Second, RCTs/quasi-randomised trials versus cross-over trials/cluster-randomised trials will be explored for potential heterogeneity). 2. Methods section–Types of studies + Types of interventions: We will not include observational studies in the meta-analyses (only a clarification and not a change). 3. Methods section–Primary outcomes: We have added All-cause mortality as a primary outcome (already included in the Summary of findings table in the published protocol but forgotten to be included in the outcome section). 4. Methods section-Searching other resources: We have added conference proceedings from the American Society of Clinical Oncology (ASCO). 5. We have added cryoprecipitate and fresh frozen plasma as potential interventions. 6. Data collection and analysis section–Assessment of heterogeneity: We have deleted the following phrase: "We will use the random-effects model for low to moderate heterogeneity" and added the phrase: "We will use the random-effects model, as we expect that all of the compared interventions do not have the same true effect." 7. We have changed the use of Review Manager 5 to Review Manager Web.

CONTRIBUTIONS OF AUTHORS

Cecilie Utke Rank: protocol development

Line Stensig Lynggaard: content input

Nina Toft: clinical input

Ove Juul Nielsen: clinical input

Wendy Stock: clinical, medical, and content input

Bodil Als-Nielsen: clinical, content, statistical, and methodological input

Thomas Leth Frandsen: clinical input

Ruta Tuckuviene: clinical input

Kjeld Schmiegelow: clinical, medical, statistical, and content input

DECLARATIONS OF INTEREST

Cecilie Utke Rank: Celgene Young Hematologist in training travel grant to attend the annual meeting of the American Society of Hematology, San Diego, 2016. This author has no conflicts of interest in relation to prophylaxis of thromboembolism in ALL patients treated with asparaginase.

Line Stensig Lynggaard: Coordinator of the clinical study NOR-GRASPALL 2016 (ClinicalTrials.gov identifier: NCT03267030); Erytech Pharma delivers the medicine and pays the costs of the study. This author do not receive payment from the company and has no conflicts of interest in relation to prophylaxis of thromboembolism in ALL patients treated with asparaginase.

Nina Toft: none known.

Ove Juul Nielsen: Member of an expert panel concerning mylotarg (Amgen) and provides consultancy questions concerning inotuzumab (Pfizer). This author has no conflicts of interest in relation to prophylaxis of thromboembolism in ALL patients treated with asparaginase.

Wendy Stock: Member of the advisory board in Jazz Pharmaceuticals, Pfizer, Astellas, Daiichi, Agios, and Kite. Payment for international speaking at meeting by Pfizer. Royalties received from UptoDate. This author has no conflicts of interest in relation to prophylaxis of thromboembolism in ALL patients treated with asparaginase.

Bodil Als-Nielsen: none known.

Thomas Leth Frandsen: none known.

Ruta Tuckuviene: Part of a cilinical trial sponsored by Daiichi Sankyo; this clinical trial has no relation to this study. This author has no conflicts of interest in relation to prophylaxis of thromboembolism in ALL patients treated with asparaginase.

Kjeld Schmiegelow: Unrestricted educational grant from Shire (2018) supporting educational acitivities on treatment-related toxicities in childhood ALL. Honorarium from Jazz Pharmaceuticals (2018) as payment for lectures. This author has no conflicts of interest in relation to prophylaxis of thromboembolism in ALL patients treated with asparaginase.

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